Immunosuppression

Introduction

Immunosuppression is immensely complex. There are so many targets, indications, and side effects, it is tough to keep everything straight. The purpose of this lesson is to give you a map of where different drugs take their effect. Learning these drugs in this context isn't helpful clinically because there is no way to predict what they will be used for based on their mechanism. When you study disease, these drugs will be mentioned in passing. These are not high-yield for studying, for test-taking, or for clinical practice, at least not until you have settled in your specialty and you use the same two immunosuppressants for what you treat. Attempting to learn all the immunosuppressants for all specialties amongst the infinite information in the rest of medicine probably isn't worth it. The names are unreliable, there aren't reliable class effects, and the indications vary. Which means every drug is a unique line item with a lot you have to know. This lesson is kept intentionally short so that you don't try to jump on the details here.

T_H0 Activation

T cells are activated by antigen-presenting cells. MHC-2 antigen binds to TCR with help of CD3 and CD4. The activation of the TCR causes a cascade of intracellular events. Two of them are of importance. First, **calcineurin** is activated, which causes the translocation of a nuclear transcription factor of activated T cells (**NFAT)** into the nucleus. NFAT leads to increased expression of **interleukin-2**. Interleukin-2 provides an autocrine signal to the T_H0 and also to any nearby lymphocytes, which also express interleukin-2 receptors. Interleukin-2 receptor activation as well as TCR activation results in the **mTOR** pathway. mTOR translocates to the nucleus and induces **proliferation**.

T_H1 Activity

A $CD4^+$ T_H1 cell is a mature T_H0. It has a TCR, CD3, and CD4. It binds antigen attached to MHC-2 from an antigen-presenting cell. It has IL-2 receptors that are activated by the release of interleukin-2 in both an autocrine mechanism from the T_H1 and from any other source of IL-2. Stimulation of T_H1 results in **IFN-γ** being released, which induces macrophage activity and IgG isotype switching.

CD8 Cytotoxic Function

$CD8^+$ cytotoxic T lymphocytes have a TCR, CD3, and CD8. They bind antigen attached to MHC-1 from any cell. They have IL-2 receptors that are activated by exogenous sources of IL-2, such as $CD4^+$ T_H0 or T_H1 cells. CD8 cytotoxic T lymphocytes secrete chemokines, such as FAS-L, granzymes, and **TNF-α**. TNF-α activates TNF-α receptors on the cell it is interacting with. This leads to apoptosis.

Nucleic Acids

Pyrimidines are synthesized through the carbamoyl-stuff-we-said-you-didn't-have-to-learn to orotic acid. Orotic acid is paired with ribose-5-phosphate. Along the way it becomes UMP, then dUMP, and ultimately to dTMP, a thymidine. "T" of DNA is made this way.

Purine salvage occurs starting with the ribose-5-phosphate. A series of reactions occurs to output a common intermediated, the name of which we are withholding. The intermediate can become dAMP ("A" of DNA) or dGMP ("G" of DNA).

The Drugs and What They Inhibit

The monoclonal antibodies end in -mab or -nab, and are used to treat advanced **autoimmune disease**. They are muromonab, daclizumab, etanercept, infliximab, and adalimumab. **Muromonab** binds CD3, which compromises the function of T_H0, T_H1, and $CD8^+$ cells. **Basiliximab** binds the IL-2 receptor, decreasing the effect of IL-2 on T_H0, T_H1, and $CD8^+$ cells. **Etanercept, infliximab, and adalimumab** are TNF-α receptor analogs and bind up TNF-α so that TNF-α receptors on cells are not activated. **Rituximab** is a CD20 antibody, useful for treating B-cell lymphomas.

The cytoplasmic acting drugs manipulate T_H0 activation and are used in **transplant medicine**. They are cyclosporine, tacrolimus, and sirolimus. Be careful, the -limus drugs share the fact that they are FK506 proteins that bind to cytoplasmic transcription factors. They are not a drug class and are not interchangeable. **Cyclosporin** is a calcineurin inhibitor, preventing the downstream expression of IL-2. **Tacrolimus** binds to NFAT in the cytoplasm, prevents its translocation to the nucleus, and also decreases expression of IL-2. **Sirolimus** binds to mTOR, prevents its translocation to the nucleus, and therefore **prohibits proliferation**.

The purine synthesis antagonists starve the cells of nucleic acids. This has the greatest effects on lymphocytes. But any tissue that is rapidly turning over, rapidly producing, or is otherwise in need of extra nucleic acids will be affected. That means these can cause pancytopenia and diarrhea. These are used interchangeably as disease-modifying agents (DMARDs) for a host of autoimmune diseases, especially those T-cell mediated. They can also be used to augment the cytoplasmic drug's effect in transplant. **6-Mercaptopurine** (it has purine in the name) inhibits upstream reactions. **Azathioprine** is a prodrug that is converted into 6-mercaptopurine. **Mycophenolate mofetil** inhibits the final step in dGMP production.

The pyrimidine synthesis antagonists are leflunomide, hydroxyurea, 5-FU, and methotrexate. **Leflunomide** is used in autoimmune diseases such as rheumatoid arthritis and affects the pyrimidine synthesis pathway upstream of orotic acid. **Hydroxyurea** is used in sickle cell disease to increase the expression of HbF to prevent the production of HbS, reducing the chance of sickle crisis. **5-fluorouracil** is a cancer drug only, targeting the last step of dTMP synthesis. **Methotrexate** is a 5-dihydrofolate reductase inhibitor which is part of a cycle necessary for thymidylate synthase to function. It is front line in the treatment of rheumatoid arthritis.

Finally, **cyclophosphamide** is an alkylating agent that binds to and destroys DNA. It is used both as a chemotherapeutic agent against cancers and as immunosuppression.

Pathways

All of the above was just enough so you can follow along with this image. It is the visual representation of this lesson. It contains everything we think you should know and nothing more. If you are looking at this image and are overwhelmed, skip it and never come back to this lesson again.

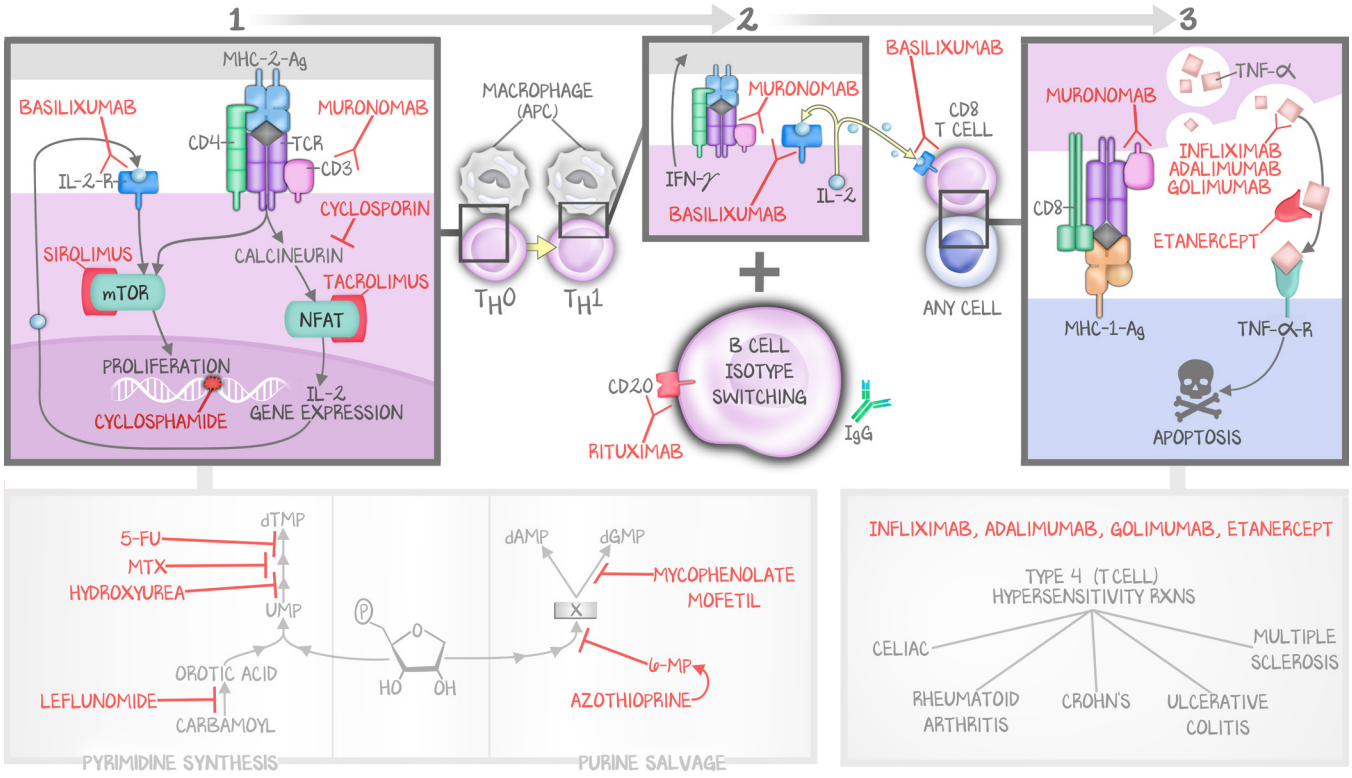

Figure 16.1: Immunosuppression Summary
In (1) the T_H0 cell is targeted by monoclonal antibodies against CD3 and IL-2, as well as the cytoplasmic signal transduction cascade inhibitors, cyclosporin, sirolimus, and tacrolimus. (2) Reminds us that CD3 and IL-2 is ubiquitous, again showing Basilixumab and Muronomab. In (3), the TNF-α inhibitors can be either in the form of a TNF-α receptor analog, etanercept, or as monoclonal antibodies—infliximab, adalimumab, and golimumab. Pyrimidine synthesis and purine salvage demonstrate the various mechanisms which metabolite immunosuppressants could work, without emphasis on any one in particular.